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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,535	10/30/2003	David T. Curiel	678503-2001.1	7880

7590 11/20/2006

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/697,535	CURIEL ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,27-32 and 34-46* is/are pending in the application.

4a) Of the above claim(s) *45 and 46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,27-32 and 34-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060928*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/28/06 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's request for an interview is noted. However, the request is premature, since Applicant is not yet aware of the issues being raised in the following Office action. Applicant is respectfully referred to MPEP 713.01, section III, and MPEP 713.02, for the appropriate bases for requesting an interview.

Election/Restrictions

Newly submitted claims 45 and 46 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:.

The originally presented invention and the newly presented invention are directed to related products (and processes using them). Related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are

mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). The originally and newly presented inventions have materially different design, where the originally presented invention involves a genetic alteration to the fiber protein to alter its tropism and that of its progeny, whereas the newly presented invention involves complexing a bifunctional ligand to an adenovirus to change its tropism but not the tropism of its progeny. Consequently, the two different types of adenovirus have different modes of operation and effect relating to the tropism of the progeny of these two different types of adenovirus. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 45 and 46 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Information Disclosure Statement

The information disclosure statement filed 9/28/06 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. No copies of documents AR and AT have been provided. It has been placed in the application file, but the information referred to therein as Documents AR and AT has not been considered. Documents AQ and AS were listed previously on the information disclosure statement of 10/7/04, and had been considered previously. Applicant is

advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a). Documents AQ and AS should not be included on any resubmission, as they were already made of record in the IDS of 10/7/04.

Claim Objections

Claim 28 is objected to because of the following informalities. In claim 28, line 2, "claim25" should be --claim 25--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 35-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 35-39 are directed to a method for reducing tumor burden in a subject by administration of a modified conditionally replicative adenovirus subtype 5 containing and expressing a nucleotide sequence encoding the fiber domain from an adenovirus subtype 3 and containing a promoter from a gene encoding "prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor, alpha-fetoprotein, vascular endothelial growth factor,

CXCR4 or survivin," which causes the adenovirus to replicate in tumor cells more efficiently than in most normal cells. Previously claim 34 had limited claims 35-39 to CRAds having a VEGF promoter operably linked to E1A. As a result of the amendment, claims 35-39 embrace embodiments where each CRAd has one of the promoters recited in claim 34 and meets the limitations of each of claims 35-39.

In the Reply of 2/24/06, Applicant indicated that support for claims 34-42 is found in Example 13 and Figs. 23-31. However, Example 13 describes the construction and use of a CRAd that is a modified human adenovirus subtype 5 (hAd5) where the E1A promoter has been replaced with a VEGF promoter region, not a promoter from a gene encoding prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor, alpha-fetoprotein, CXCR4 or survivin. The reply of 9/28/06 does not indicate where the original specification supports a hAd5-based CRAd having a prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor, alpha-fetoprotein, CXCR4 or survivin gene promoter operably linked to the E1A region in conjunction with a chimeric hAd5 fiber with a knob domain from hAd3 that will suppress tumor growth of non-small cell lung cancer, ovarian cancer, gastric cancer and pancreatic cancer, and that does not cause hepatic injury. It is Applicant's burden to indicate how and where the original application supports new claim limitations, MPEP 714.02, last sentence of the third paragraph from the end, and 2163.06 (I), last sentence.

Consequently, the original specification does not provide evidence that the broadly claimed inventions of claims 35-39 had been contemplated or possessed by the inventors at the time the application was filed. Due to the amendment to claim 34, claims 35-39 now include impermissible new matter.

Claims 43 and 44 are directed to a method for reducing tumor burden in a subject by administration of a modified conditionally replicative "contains and expresses a nucleotide sequence encoding the fiber knob domain of the canine adenovirus type 2," and has a promoter from a gene encoding "prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor, alpha-fetoprotein, vascular endothelial growth factor, CXCR4 or survivin", which causes the adenovirus to replicate in tumor cells more efficiently than in most normal cells.

In the Reply of 2/24/06, Applicant indicates that support for these claims are found in Example 14 and Figs. 32-35. However, Example 14 describes a prophetic CRAd that is a modified human adenovirus subtype 5 (hAd5) where the gene encoding the fiber protein of the CRAd has the knob domain coding region replaced with a sequence encoding the knob domain of canine Ad2 (Cad2). Also, the CRAd contains an CXCR4 or survivin promoter, specifically, that replaces E1A promoter (Fig. 34). The reply of 9/28/06 does not indicate where the original specification supports a hAd5-based CRAd having a prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor, alpha-fetoprotein, or vascular endothelial growth factor gene promoter in conjunction with a chimeric hAd5 fiber with a knob domain from CAd2. It is Applicant's burden to indicate how and where the original application supports new claim limitations, MPEP 714.02, last sentence of the third paragraph from the end, and 2163.06 (I), last sentence.

This originally disclosed CRAd genome does not broadly contain a promoter from a gene encoding prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor,

alpha-fetoprotein, or vascular endothelial growth factor. The only promoters described for this embodiment are the CXCR4 or survivin promoters.

Consequently, the original specification does not provide evidence that the broadly claimed inventions of claims 43-44 had been contemplated or possessed by the inventors at the time the application was filed. The newly amended claims therefore contain impermissible new matter. It is suggested that the claims be amended to accurately reflect the original description of these embodiments, i.e. by deleting "prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor, alpha-fetoprotein, vascular endothelial growth factor".

Claims 34-44 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34-44 remain incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are the relationship between the hAd3 or Cad2 fiber knob domain and their coding sequences and the modified fiber protein of the CRAd and its coding sequence. As disclosed in the specification, the coding sequences of the fiber knob domains replace the coding sequence of the fiber knob domain of a Coxsackie-adenovirus receptor-dependent adenovirus on which the CRAd is based, e.g. hAd5. Such a chimeric fiber protein is encoded and expressed by the genome of the CRAd. Claims 34 and 43 should be amended to indicate that the fiber protein of the CRAd is a chimeric

fiber protein comprising the hAd3 or the Cad2 fiber knob domain, respectively, and that CRAd contains and expresses a nucleotide sequence encoding the chimeric fiber protein.

Claims 34 and 43 have been amended to indicate that the adenovirus encodes and expresses the knob domain, but the claims still provide no nexus between the knob domain and the fiber protein or the sequences encoding both.

Claims 34-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34-44 remain incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationship is the relationship between the deletion of the E1A promoter and the insertion of the "promoter region". As written, the claims do not require that the insertion of the promoter region be made where the E1A promoter was deleted. The claim should be amended to clearly indicate that the E1A promoter is replaced with the "promoter region".

Claim Rejections - 35 USC § 102

Claims 25, 28, 29, 34, 35 and 39 remain rejected under 35 U.S.C. 102(a) as being clearly anticipated by Takayama et al. Mol. Ther. 7(5, Part 2): S420, abstract 1089, May 2003, as evidenced by Curiel et al., WO 00/67576, for the reasons of record set forth in the Office action of 5/31/06.

Takayama discloses treatment of lung cancer with a CRAd comprising an E1 region under control of the human VEGF promoter and modification of its fiber by replacement of the knob with that of Ad3. Curiel (see entire document, especially pages 4-6) is illustrative of the state of the CRAd art at the time Takayama was published, and shows that at this time one of skill in this art was aware of how to prepare CRAds and administer them in treatment of cancer. Curiel teaches, for example, that in CRAds having E1A under control of a tumor specific promoter the E1A promoter is replaced with the tumor specific promoter. As indicated in the instant specification, the VEGF promoter is not efficient at directing transcription in normal liver cells, consequently limitation recited in claim 39 is an inherent characteristic of the this particular CRAd, which is the same CRAd as disclosed in Example 13.

Claims 25, 26, 28, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Curiel, D.T. (Proc. Amer. Assoc. Cancer Res. Ann. Meet. 43: 662-663, abstract 3287, March 2002), as evidenced by Curiel et al., WO 00/67576, for the reasons of record set forth in the Office action of 5/31/06.

Curiel (2002) generally describes CRAd for use in treatment of cancer comprising a fiber modified by insertion of ligands into the HI loop or by replacement with the knob of an adenovirus of another serotype, wherein the E1 region of the CRAd is placed under control of a tumor specific promoter, such as the VEGF promoter, and the CRAd may contain a heterologous therapeutic gene, encoding a heat shock protein that increases increase potency of the CRAd. WO 00/67576 is illustrative of the state of the CRAd art at the time Curiel was published, and shows that at this time one of skill in this art was aware of how to prepare CRAds and administer

them in treatment of cancer (see entire document, especially pages 4-6). WO 00/67576 teaches, for example, that in CRAds having E1A under control of a tumor specific promoter the E1A promoter is replaced with the tumor specific promoter.

Applicant's arguments filed 9/28/06 have been fully considered but they are not persuasive. Applicant asserts that Takayama and Curiel (abstract 3287) are not enabled, and that Curiel, WO 00/67576, does not cure the defect. In response, Applicant is reminded that prior art is presumed to be enabling, MPEP 2121, and Applicant has provided no evidence to suggest that one of skill in the adenoviral art required more information to make and use the CRAds of Takayama and Curiel (abstract 3287) without undue experimentation than was presented in these references. WO 00/67576 was cited as evidence (e.g. pages 4 and 6) that one in the adenoviral vector art was well aware, for example, of how to transcriptionally target CRAds by substituting the E1A promoter with a tumor specific promoter and how to genetically modify the tropism of an adenovirus by genetically modifying the fiber gene, and the protein encoded thereby.

Claim Rejections - 35 USC § 103

Claims 25, 27, 30-32, 34, and 39-42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Takayama et al. (Mol. Ther. 7(5, Part 2): S420, abstract 1089), May 2003, in view of Curiel et al., WO 00/67576, for the reasons of record set forth in the Office action of 5/31/06.

Claims 25, 27, 30-32, 34 and 39-42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Curiel, D.T. (Proc. Amer. Assoc. Cancer Res. Ann. Meet. 43: 662-663, abstract 3287, March 2002) in view of Curiel et al., WO 00/67576, for the reasons of record set forth in the Office action of 5/31/06.

Claims 25 and 27-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Molnar-Kimber, WO 01/23004 in view of Curiel et al., WO 00/67576, for the reasons of record set forth in the Office action of 5/31/06.

Claims 36-38 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Takayama et al. Mol. Ther. 7(5, Part 2): S420, abstract 1089, May 2003, as evidenced by Curiel et al., WO 00/67576, as applied to claims 25, 28, 29, 34, 35 and 39 above, and further in view of Takayama et al., Mol. Ther. 5(5, Part 2): S268, abstract 821, May 2002, for the reasons of record set forth in the Office action of 5/31/06.

Claims 35-38 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Curiel, D.T. (Proc. Amer. Assoc. Cancer Res. Ann. Meet. 43: 662-663, abstract 3287, March 2002) in view of Curiel et al., WO 00/67576, as applied to claims 25, 27, 30-32, 34 and 39-42 above, and further in view of Takayama et al., Mol. Ther. 5(5, Part 2): S268, abstract 821, May 2002, for the reasons of record set forth in the Office action of 5/31/06.

Applicant's arguments filed 9/28/06 have been fully considered but they are not persuasive. After a summary of pertinent case law and the grounds of rejection, Applicant simply asserts (Reply, page 15) that the references do not teach or suggest all the limitations of the claims, specifically that they do not teach the CXCR4 or survivin promoters. In response, none of the claims are limited to embodiments where either of these two promoters are used, but also include the VEGF promoter, for example, as an alternative. Also, Molnar-Kimble teaches to use the survivin promoter *inter alia.* There is no legal requirement that prior art cited in a rejection under 35 USC 102 or 103 describe all embodiments readable on a broad claim. The cited prior art alone or in combination need only describe at least one species readable on a broad claim. In this case, the cited combinations of prior art documents describe all the limitations of at least one embodiment readable on the rejected claims for the reasons of record.

Double Patenting

Claims 25, 27-32, and 34-42 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 9-12 of U.S. Patent No. 6,824,771 in view of Curiel et al., WO 00/67576; Takayama et al. Mol. Ther. 7(5, Part 2): S420, abstract 1089, May 2003; and Takayama et al., Mol. Ther. 5(5, Part 2): S268, abstract 821, May 2002, for the reasons of record set forth in the Office action of 5/31/06.

Applicant has not provided any argument in traverse of this rejection, and indicated that if the claims are otherwise allowable, a terminal disclaimer will be filed. This rejection will not be held in abeyance, nor will it be withdrawn until a terminal disclaimer is filed or the claims are amended to overcome the rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Scott D. Priebe

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